

# 87939 SEARCH REQUEST FORM

Access DB#

Scientific and Technical Information Center

Requester's Full Name: Konak M. George Examiner #: 77560 Date: 3/3/03  
 Art Unit: 1616 Phone Number 308-4646 Serial Number: 10/033,632  
 Mail Box and Bldg/Room Location: \_\_\_\_\_ Results Format Preferred (circle): PAPER DISK E-MAIL  
2 D 19 2 D 14

If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*  
 Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Drugs for Spinal Anesthesia  
 Inventors (please provide full names): Timothy J. Brennan

Earliest Priority Filing Date: 12/26/01

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search:

6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoguinolinol  
 -3-carboxylic <sup>acid</sup> ~~acid~~ according to claim 1. If found please  
 search for use as a pharmaceutical, especially  
 as an anesthesia.

LS Kishin  
 Acting for TK Page

Thanks

Konak G.

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Searcher: <u>Shelton</u>	Type of Search: _____	Vendors and cost where applicable: _____
Searcher Phone #: <u>308-4499</u>	NA Sequence (#) _____	STN _____
Searcher Location: _____	AA Sequence (#) _____	Dialog _____
Date Searcher Picked Up: _____	Structure (#) _____	Questel/Orbit _____
Date Completed: <u>3/7/03</u>	Bibliographic _____	Dr.Link _____
Searcher Prep & Review Time: _____	Litigation _____	Lexis/Nexis _____
Clerical Prep Time: _____	Fulltext _____	Sequence Systems _____
Online Time: _____	Patent Family _____	WWW/Internet _____
	Other _____	Other (specify) _____

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FILE COVERS 1907 - 7 Mar 2003 VOL 138 ISS 11  
FILE LAST UPDATED: 6 Mar 2003 (20030306/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d stat que  
L39 40 SEA FILE=REGISTRY ABB=ON PLU=ON TETRAZOL?(L)ETHYL(L)DECA?(L)C  
ARBOX?  
L40 214532 SEA FILE=REGISTRY ABB=ON PLU=ON 3(W)CARBOX?  
L41 8 SEA FILE=REGISTRY ABB=ON PLU=ON L39 AND L40  
L49 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L41

=> d ibib abs hitrn 149 1

L49 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2002:521728 HCAPLUS  
DOCUMENT NUMBER: 137:93757  
TITLE: Preparation of sulfonylamino- and  
azolylypyrrolidinylmethylisoquinolinecarboxylates as  
excitatory amino acid receptor antagonists.  
INVENTOR(S): Bleisch, Thomas John; Filla, Sandra Ann; Ornstein,  
Paul Leslie  
PATENT ASSIGNEE(S): Eli Lilly and Company, USA  
SOURCE: PCT Int. Appl., 94 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2002053556	A2	20020711	WO 2001-US45862	20011220
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, FL, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU			

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,  
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

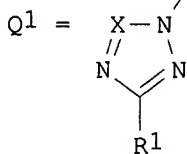
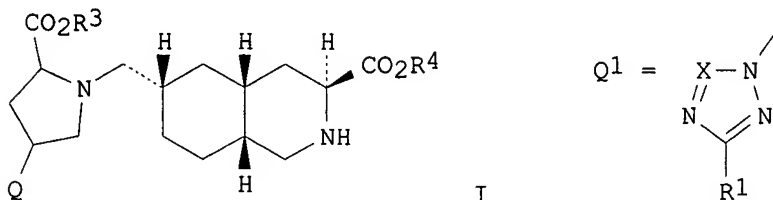
PRIORITY APPLN. INFO.:

US 2001-259922P P 20010105

OTHER SOURCE(S):

MARPAT 137:93757

GI



AB Title compds. [I; R1 = H, alkyl, alkoxy, cycloalkyl, SO2R2, SR2, CH2SR2, aryl, aralkyl, (substituted) aryl; R2 = alkyl; R3, R4 = H, alkyl, alkenyl, alkylaryl, alkylcycloalkyl, alkylalkylamino, alkylpyrrolidinyl, alkylpiperidinyl, alkylmorpholinyl; Q = Q1, R5YSO2NR6; R5 = alkyl, CF3, (substituted) aryl; R6 = H, alkyl, alkylaryl; Y = (CH2)n; n = 0-3; with a proviso], were prepd. for, e.g., treatment of migraine (no data). Thus, Et (3S,4aR,6S,8aR)-6-[[[(3S,5S)-5-(ethoxycarbonyl)-3-hydroxypyrrolidinyl]methyl]-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (prepn. given), tetrazole, and Ph3P in THF at 0.degree. were treated dropwise with di-Et azodicarboxylate followed by stirring for 18 h at room temp. to give 31% tetrazolylpyrrolidine deriv., which was heated in 6N HCl at 95.degree. for 18 h to give 100% (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-carboxy-4-(tetrazol-1-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid dihydrochloride.

IT **441053-86-7P**, (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-ethoxycarbonyl-4-(5-methyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-87-8P**, (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-ethoxycarbonyl-4-(5-adamantyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-88-9P**, (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-ethoxycarbonyl-4-(5-cyclopentyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-89-0P**, (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-ethoxycarbonyl-4-(5-propyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-90-3P**, (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-ethoxycarbonyl-4-(5-phenyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride **441053-92-5P**, (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-carboxy-4-[5-(1,1-dimethylethyl)-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid **441053-97-0P**, (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-carboxy-4-(5-ethyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid **441053-98-1P**, (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-carboxy-4-[5-isopropyl-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid dihydrochloride

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of sulfonylamino- and azolylpyrrolidinylmethylisoquinolinecarboxylates as excitatory amino acid receptor antagonists)

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=&gt; fil caold

FILE 'CAOLD' ENTERED AT 10:33:56 ON 07 MAR 2003  
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FILE COVERS 1907-1966

FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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=&gt; s 141

L50 0 L41

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FILE 'REGISTRY' ENTERED AT 10:34:08 ON 07 MAR 2003  
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 5 MAR 2003 HIGHEST RN 497055-63-7  
DICTIONARY FILE UPDATES: 5 MAR 2003 HIGHEST RN 497055-63-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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L41 ANSWER 1 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 441053-98-1 REGISTRY

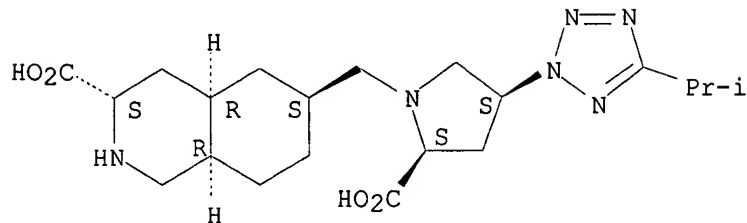
CN 3-Isoquinolinecarboxylic acid, 6-[[[(2S,4S)-2-carboxy-4-[5-(1-methylethyl)-2H-tetrazol-2-yl]-1-pyrrolidinyl)methyl]decahydro-, dihydrochloride, (3S,4aR,6S,8aR)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN (3S,4AR,6S,8aR)-6-[[[(2S,4S)-2-carboxy-4-[5-isopropyl-2H-tetrazol-2-yl]-1-pyrrolidinyl)methyl]decahydroisoquinoline-3-carboxylic acid dihydrochloride

FS STEREOSEARCH  
 MF C20 H32 N6 O4 . 2 Cl H  
 SR CA  
 LC STN Files: CA, CAPLUS

Absolute stereochemistry.



● 2 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

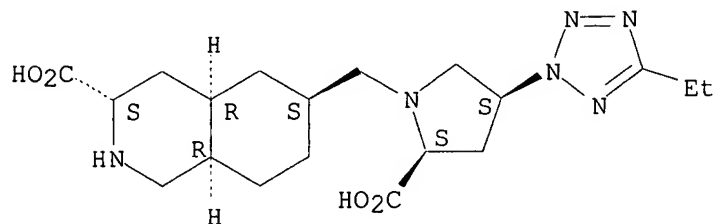
L41 ANSWER 2 OF 8 REGISTRY COPYRIGHT 2003 ACS  
 RN 441053-97-0 REGISTRY  
 CN 3-Isoquinolinecarboxylic acid, 6-[[ (2S,4S)-2-carboxy-4-(5-ethyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, (3S,4aR,6S,8aR)- (9CI)  
 (CA INDEX NAME)

OTHER NAMES:

CN (3S,4aR,6S,8aR)-6-[[ (2S,4S)-2-carboxy-4-(5-ethyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid

FS STEREOSEARCH  
 MF C19 H30 N6 O4  
 SR CA  
 LC STN Files: CA, CAPLUS

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1962 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 3 OF 8 REGISTRY COPYRIGHT 2003 ACS  
 RN 441053-92-5 REGISTRY  
 CN 3-Isoquinolinecarboxylic acid, 6-[[ (2S,4S)-2-carboxy-4-[5-(1,1-dimethylethyl)-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydro-,

(3S,4aR,6S,8aR) - (9CI) (CA INDEX NAME)

## OTHER NAMES:

CN (3S,4aR,6S,8aR)-6-[[ (2S,4S)-2-carboxy-4-[5-(1,1-dimethylethyl)-2H-tetrazol-2-yl]-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid

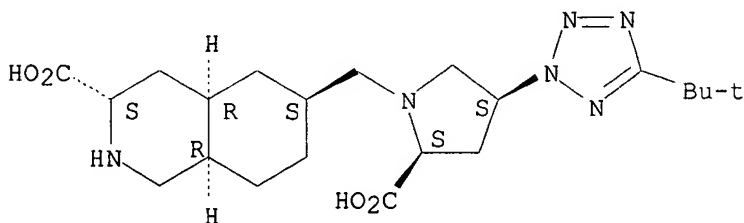
FS STEREOSEARCH

MF C21 H34 N6 O4

SR CA

LC STN Files: CA, CAPLUS

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

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1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 4 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 441053-90-3 REGISTRY

CN 3-Isoquinolinecarboxylic acid, 6-[[ (2S,4S)-2-(ethoxycarbonyl)-4-(5-phenyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR) - (9CI) (CA INDEX NAME)

## OTHER NAMES:

CN (3S,4aR,6S,8aR)-6-[[ (2S,4S)-2-ethoxycarbonyl-4-(5-phenyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride

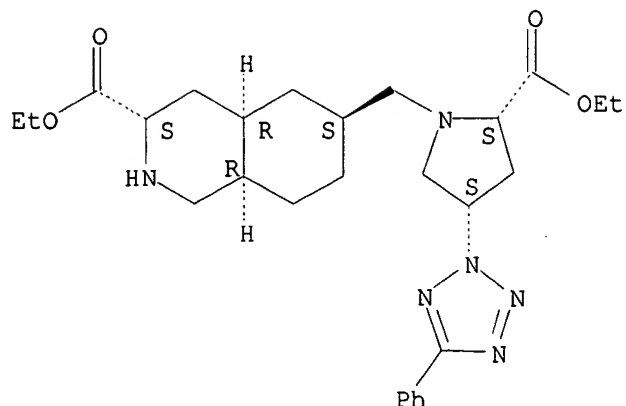
FS STEREOSEARCH

MF C27 H38 N6 O4 . 2 Cl H

SR CA

LC STN Files: CA, CAPLUS

Absolute stereochemistry.



● 2 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 5 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 441053-89-0 REGISTRY

CN 3-Isoquinolinecarboxylic acid, 6-[[[(2S,4S)-2-(ethoxycarbonyl)-4-(5-propyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-ethoxycarbonyl-4-(5-propyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride

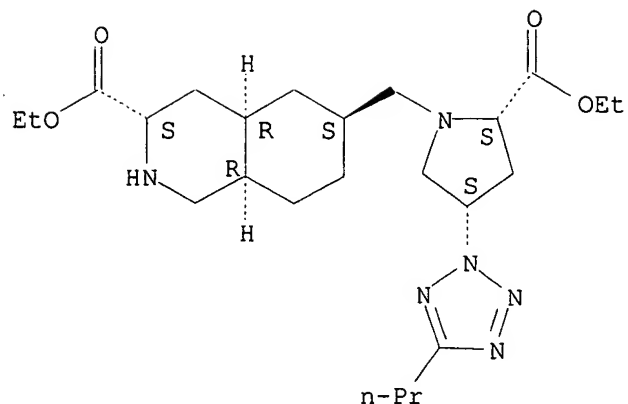
FS STEREOSEARCH

MF C24 H40 N6 O4 . 2 Cl H

SR CA

LC STN Files: CA, CAPLUS

Absolute stereochemistry.



● 2 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 6 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 441053-88-9 REGISTRY

CN 3-Isoquinolinecarboxylic acid, 6-[[[(2S,4S)-4-(5-cyclopentyl-2H-tetrazol-2-yl)-2-(ethoxycarbonyl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR)-(9CI) (CA INDEX NAME)

OTHER NAMES:

CN (3S,4aR,6S,8aR)-6-[[[(2S,4S)-2-ethoxycarbonyl-4-(5-cyclopentyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride

FS STEREOSEARCH

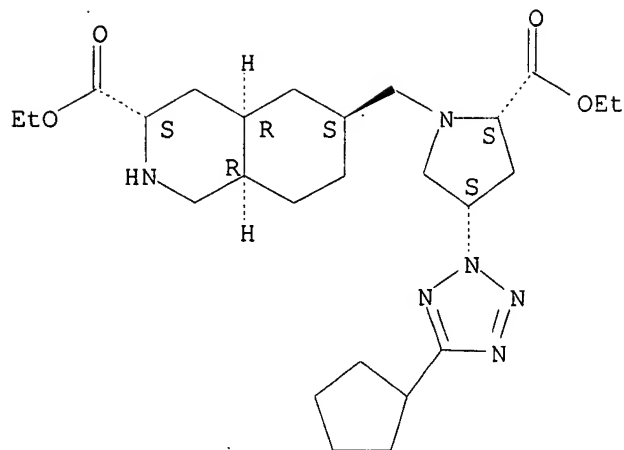
MF C26 H42 N6 O4 . 2 Cl H

SR CA

LC STN Files: CA, CAPLUS

Absolute stereochemistry.





● 2 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 7 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 441053-87-8 REGISTRY

CN 3-Isoquinolinecarboxylic acid, 6-[[[(2S,4S)-2-(ethoxycarbonyl)-4-(5-tricyclo[3.3.1.1.3,7]dec-1-yl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN (3S,4AR,6S,8aR)-6-[[[(2S,4S)-2-ethoxycarbonyl-4-(5-adamantyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride

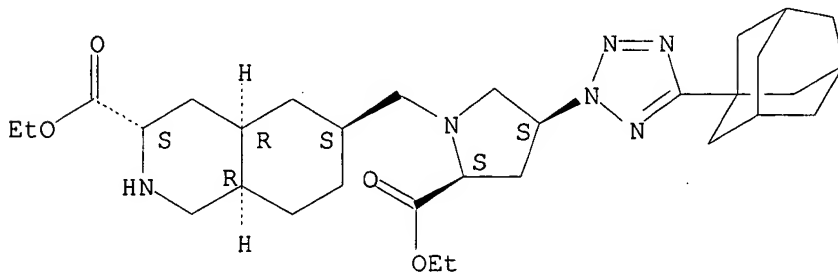
FS STEREOSEARCH

MF C31 H48 N6 O4 . 2 Cl H

SR CA

LC STN Files: CA, CAPLUS

Absolute stereochemistry.



2 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

L41 ANSWER 8 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 441053-86-7 REGISTRY

CN 3-Isoquinolinecarboxylic acid, 6-[[ (2S,4S)-2-(ethoxycarbonyl)-4-(5-methyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydro-, ethyl ester, dihydrochloride, (3S,4aR,6S,8aR)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN (3S,4aR,6S,8aR)-6-[[ (2S,4S)-2-ethoxycarbonyl-4-(5-methyl-2H-tetrazol-2-yl)-1-pyrrolidinyl]methyl]decahydroisoquinoline-3-carboxylic acid ethyl ester dihydrochloride

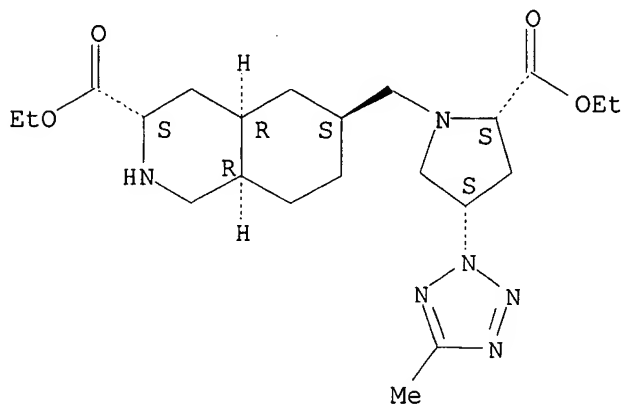
FS STEREOSEARCH

MF C22 H36 N6 O4 . 2 Cl H

SR CA

LC STN Files: CA, CAPLUS

Absolute stereochemistry.



● 2 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:93757

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FILE COVERS 1907 - 7 Mar 2003 VOL 138 ISS 11

FILE LAST UPDATED: 6 Mar 2003 (20030306/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L39	40	SEA FILE=REGISTRY	ABB=ON	PLU=ON	TETRAZOL? (L) ETHYL (L) DECA? (L) C
		ARBOX?			
L40	214532	SEA FILE=REGISTRY	ABB=ON	PLU=ON	3 (W) CARBOX?
L41	8	SEA FILE=REGISTRY	ABB=ON	PLU=ON	L39 AND L40
L46	323	SEA FILE=HCAPLUS	ABB=ON	PLU=ON	DECAHYDROISOQUIN?
L49	1	SEA FILE=HCAPLUS	ABB=ON	PLU=ON	L41
L53	66	SEA FILE=HCAPLUS	ABB=ON	PLU=ON	L46 AND 3 (W) CARBOX?
L54	40	SEA FILE=HCAPLUS	ABB=ON	PLU=ON	L53 AND TETRA?
L55	11	SEA FILE=HCAPLUS	ABB=ON	PLU=ON	L54 AND TETRAZOLE (W) 5
L56	11	SEA FILE=HCAPLUS	ABB=ON	PLU=ON	L55 NOT L49

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=> d ibib abs hitrn 156 1-11

L56 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:806928 HCAPLUS

DOCUMENT NUMBER: 134:161346

TITLE: Role of AMPA and GluR5 kainate receptors in the development and expression of amygdala kindling in the mouse

AUTHOR(S): Rogawski, M. A.; Kurzman, P. S.; Yamaguchi, S.-i.; Li, H.

CORPORATE SOURCE: Neuronal Excitability Section, Epilepsy Research Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892-1408, USA

SOURCE: Neuropharmacology (2000), Volume Date 2001, 40(1), 28-35

CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The role of AMPA and GluR5-contg. kainate receptors in the development and expression of amygdala kindling was examd. using the selective 2,3-benzodiazepine AMPA receptor antagonist GYKI 52466 [(1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine] and the **decahydroisoquinoline** mixed AMPA receptor and GluR5 kainate receptor antagonist LY293558 ((3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]**decahydroisoquinoline-3-carboxylic acid**)). Administration of GYKI 52466 (5-40 mg/kg, i.p.) and LY293558 (10-40 mg/kg, i.p.) prior to daily kindling stimulation in mice produced a dose-dependent suppression of the rate of development of behavioral kindled seizure activity and reduced the duration of the stimulation-induced electrog. afterdischarge. In drug-free stimulation sessions after the initial drug-treatment sessions, there was an acceleration in the rate of kindling development compared with the rate during the preceding drug-administration period; the "rebound" rate was also greater than the kindling rate in saline-treated control animals. In fully kindled animals, both GYKI 52466 and LY293558 produced a dose-dependent suppression of evoked seizures (ED50, 19.3 and 16.7 mg/kg, resp.). Although AMPA receptors appear to be crit. to the expression of kindled seizures, since kindling development progressed despite the suppression of behavioral seizure activity, AMPA receptors are less important to the kindling process. LY293558 was modestly less effective at suppressing behavioral seizures during kindling and was not superior to GYKI 52466 in retarding the overall extent of kindling development, indicating that GluR5 kainate receptors do not contribute to epileptogenesis in this model.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:304166 HCAPLUS

DOCUMENT NUMBER: 133:218055

TITLE: Kainate receptor-mediated activation of the AP-1 transcription factor complex in cultured rat cerebellar granule cells

AUTHOR(S): Kovacs, A. D.; Cebers, G.; Liljequist, S.

CORPORATE SOURCE: Division of Drug Dependence Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Swed.

SOURCE: Brain Research Bulletin (2000), 52(2), 127-133  
CODEN: BRBUDU; ISSN: 0361-9230

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The sequence-specific DNA-binding activity of the AP-1 transcription factor complex was measured in cultured rat cerebellar granule cells by electrophoretic mobility shift assay. A low concn. of kainate (KA; 10 .mu.M), but not .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA; 10 .mu.M), enhanced DNA-binding of the AP-1 transcription factor in cultures pretreated with Con A (Con A), to prevent KA receptor desensitization. In the presence of cyclothiazide (an inhibitor of AMPA receptor desensitization), KA (10 .mu.M) caused only a slight increase of AP-1 DNA-binding, in contrast to the 3-fold enhancement produced by AMPA (10 or 30 .mu.M) or by a higher concn. of KA (30 .mu.M), suggesting that the effect of KA, in the presence of Con A, is mediated by activation of putative KA receptors. To confirm this, the effects of the AMPA receptor-selective, non-competitive antagonist, 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 53655; 50 .mu.M), the mixed AMPA/KA receptor competitive antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 50 .mu.M), and the AMPA and GluR5 KA receptor competitive antagonist, (-) (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5

-yl)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid monohydrate (LY 326325; 100 .mu.M), were examd. on AMPA- and KA-induced AP-1 activation, resp. The authors results suggest that stimulation of native KA receptors is responsible for the obsd. KA-specific activation of the AP-1 transcription factor complex.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:704431 HCAPLUS

DOCUMENT NUMBER: 131:317686

TITLE: Synergistic neuroprotective effects by combining an NMDA or AMPA receptor antagonist with nitric oxide synthase inhibitors in global cerebral ischemia  
AUTHOR(S): Hicks, C. A.; Ward, M. A.; Swettenham, J. B.; O'Neill, M. J.

CORPORATE SOURCE: Lilly Research Centre, Eli Lilly & Company, Windlesham, Surrey, UK

SOURCE: European Journal of Pharmacology (1999), 381(2/3), 113-119

CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have investigated the neuroprotective effects of combining an NMDA or AMPA receptor antagonist with a nitric oxide synthase (NOS) inhibitor in the gerbil model of global cerebral ischemia. Ischemia was induced by occlusion of the common carotid arteries for 5 min. (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801, 2.5 mg/kg i.p.) or (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)]decahydroisoquinoline-3-carboxylic acid (LY293558, 20 mg/kg i.p.) and 7-nitroindazole (25 mg/kg i.p.) or N-[4-(2-((3-chlorophenyl)methyl)amino)ethyl] phenyl]-2-thiophenecarboximidamide dihydrochloride (ARL17477, 25 mg/kg i.p.) were administered alone or in combination (i.e., MK-801 with 7-nitroindazole or ARL17477 or LY293558 with 7-nitroindazole or ARL17477). In the present studies, both MK-801 and LY293558 provided significant degree of neuroprotection, while 7-nitroindazole and ARL17477 also provided some neuroprotection, which failed to reach significance in every case. However, the combination of MK-801 with 7-nitroindazole or ARL17477 provided 21% or 44% greater protection than the total protection or either alone. Likewise, the combination of LY293558 with 7-nitroindazole or ARL17477 provided 14.5% and 35% greater protection than total protection of either compd. alone. These results indicate that several pathways contribute to ischemic cell death and combining excitatory amino antagonists and NOS inhibitors provides greater protection than either alone. Therefore, combination therapy should be considered as an approach for treating ischemic conditions.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:693075 HCAPLUS

DOCUMENT NUMBER: 131:335363

TITLE: NMDA receptor antagonism, but not AMPA receptor antagonism attenuates induced ischemic tolerance in the gerbil hippocampus

AUTHOR(S): Bond, Ann; Lodge, David; Hicks, Caroline A.; Ward, Mark A.; O'Neill, Michael J.

CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Company, Surrey, GU20 6PH, UK

SOURCE: European Journal of Pharmacology (1999), 380(2/3), 91-99

CODEN: EJPHAZ; ISSN: 0014-2999  
 PUBLISHER: Elsevier Science B.V.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Recent studies have shown that a brief "pre-conditioning" ischemic insult reduces the hippocampal cell death caused by a subsequent more severe test insult. In the present studies, the authors have examd. the effects of the non-competitive NMDA receptor antagonist ((5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine, MK-801) a competitive NMDA receptor antagonist, LY202157, AMPA receptor antagonist ((3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)]**decahydroisoquinoline-3-carboxylic acid**, LY293558), a non-competitive AMPA receptor antagonist ((-)-1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-acetyl-2,3-benzodiazepine, LY300164), and a mixed NMDA / AMPA receptor antagonist, LY246492, in a gerbil model of ischemic tolerance. Ischemic tolerance was induced by subjecting gerbils to a 2-min "pre-conditioning" ischemia (bilateral carotid occlusion) 2 days prior to a 3-min test ischemia. The effects of MK-801 (2 mg/kg i.p.), LY293558 (20 mg/kg i.p., followed by 4 .times. 10 mg/kg at 3 h intervals), LY300164 (4 .times. 10 mg/kg i.p. at 1 h intervals), LY246492 (40 mg/kg i.p., followed by 4 .times. 20 mg/kg i.p. at 3 h intervals) and LY202157 (30 mg/kg i.p., followed by 4 .times. 15 mg/kg i.p. at 2 h intervals) were then examd. in this model. Initial dosing commenced 30 min prior to the 2-min "pre-conditioning" ischemia. Results indicated that a 2-min "pre-conditioning" ischemia produced ischemic tolerance in all cases. The non-competitive NMDA receptor antagonist, MK-801, produced a significant (P < 0.01) redn. in the induced tolerance, while the competitive NMDA receptor antagonist, LY202157, also attenuated (P < 0.05) the induction of tolerance. In contrast, two AMPA receptor antagonists (LY293558 and LY300164) and a mixed NMDA/AMPA receptor antagonist (LY246492) had no effect on the induction of tolerance. These results suggest that NMDA receptor activation, but not AMPA receptor activation is involved in the phenomenon of ischemic tolerance.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:481992 HCAPLUS  
 DOCUMENT NUMBER: 127:170899  
 TITLE: (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]**decahydroisoquinoline-3-carboxylic acid** (LY293558) and its racemate (LY215490): a selective and competitive AMPA/kainate receptor antagonist  
 AUTHOR(S): Lodge, David; Schoepp, Darryle D.  
 CORPORATE SOURCE: Lilly Res. Centre Ltd., Eli Lilly & Co., Surrey, GU20 6PH, UK  
 SOURCE: Excitatory Amino Acids: Clinical Results with Antagonists (1997), 81-87, 129-152. Editor(s): Herrling, P. L. Academic: London, UK.  
 CODEN: 64UIAO  
 DOCUMENT TYPE: Conference; General Review  
 LANGUAGE: English

AB A review with over 550 refs. During the structure-activity development of series of **decahydroisoquinoline**-based N-methyl-D-aspartate (NMDA) antagonists, some compds. in the series showed activity at .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Of these, (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]**decahydroisoquinoline-3-carboxylic acid** (LY293558) (Fig. 1) was one of the most potent and selective for AMPA receptors in vitro and in vivo. LY215490 is the racemic mixt. LY293558 is centrally active following parenteral administration in animals, with

no NMDA receptor antagonist activity at in vivo doses which block AMPA receptors, and a pharmacol. consistent with effects of other known AMPA antagonists. LY293558 possesses neuroprotectant activity against AMPA- and ischemia-induced neuronal injury in multiple animal models including focal ischemia in the rat and cat, and spinal ischemia in the rabbit. Thus, LY293558 may have clin. utility as a neuroprotectant in patients subjected to an ischemic neuronal event that involves glutamate excitotoxicity.

L56 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:706664 HCAPLUS  
DOCUMENT NUMBER: 126:1010  
TITLE: Selective protection against AMPA- and kainate-evoked neurotoxicity by (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid (LY293558) and its racemate (LY215490)  
AUTHOR(S): Schoepp, D. D.; Salhoff, C. R.; Fuson, K. S.; Sacca, A. I.; Tizzano, J. P.; Ornstein, P. L.; May, P. C.  
CORPORATE SOURCE: Lilly Research Labs., Eli Lilly Co., Indianapolis, IN, USA  
SOURCE: Journal of Neural Transmission (1996), 103(8-9), 905-916  
CODEN: JNTRF3; ISSN: 0300-9564  
PUBLISHER: Springer  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Glutamate receptor-mediated excitotoxicity is linked to the activation of multiple receptors including those activated by .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate. In this study, the novel glutamate receptor antagonist, as its active isomer (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid ((-)-LY293558) and its .+-. racemate (LY215490), was examd. for neuroprotectant effects against excitotoxic injury in vitro and in vivo. This agent selectively protected against AMPA and kainate injury in cultured primary rat hippocampal neurons, an in vivo rat striatal neurotoxicity model, and against agonist-evoked seizures in mice. Thus, (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid represents a novel receptor selective and potent systemically active AMPA/kainate receptor antagonist for exploring neuroprotection via non-NMDA receptor mechanisms.

L56 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:271752 HCAPLUS  
DOCUMENT NUMBER: 125:320  
TITLE: Structure-Activity Studies of 6-Substituted Decahydroisoquinoline-3-carboxylic Acid AMPA Receptor Antagonists. 2. Effects of Distal Acid Bioisosteric Substitution, Absolute Stereochemical Preferences, and in Vivo Activity  
AUTHOR(S): Ornstein, Paul L.; Arnold, M. Brian; Allen, Nancy K.; Bleisch, Thomas; Borromeo, Peter S.; Lugar, Charles W.; Leander, J. David; Lodge, David; Schoepp, Darryle D.  
CORPORATE SOURCE: Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center Indianapolis, IN, 46285, USA  
SOURCE: Journal of Medicinal Chemistry (1996), 39(11), 2232-44  
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB We have explored the excitatory amino acid antagonist activity in a series of **decahydroisoquinoline-3-carboxylic** acids, and within this series found the potent and selective AMPA antagonist (3SR,4aRS,6RS,8aRS)-6-[2-(1H-**tetrazol**-5-yl)ethyl]**decahydroisoquinoline-3-carboxylic** acid (I). In this and the preceding paper, we looked at the structure-activity relationships for AMPA antagonist activity in this series of compds. We have already shown that I had the optimal stereochem. array and that AMPA antagonist activity was maximized for a two-carbon spacer sepg. a **tetrazole** from the bicyclic nucleus. In this paper, we explored the effects of varying the distal acid and the abs. stereochem. preferences of many of these analogs. We looked at a variety of different acid bioisosteres, including 5-membered heterocyclic acids such as **tetrazole**, 1,2,4-triazole, and 3-isoxazolone; carboxylic, phosphonic, and sulfonic acid; and acyl sulfonamides. Compds. were evaluated in rat cortical tissue for their ability to inhibit the binding of radioligands selective for AMPA ([3H]AMPA), NMDA ([3H]CGS 19755), and kainic acid ([3H]kainic acid) receptors and for their ability to inhibit depolarizations induced by AMPA (40 .mu.M), NMDA (40 .mu.M), and kainic acid (10 .mu.M). A no. of compds. from this and the preceding paper were also evaluated in mice for their ability to block maximal electroshock-induced convulsions and ATPA-induced rigidity in mice.

L56 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:240710 HCAPLUS  
DOCUMENT NUMBER: 124:307404  
TITLE: Pharmacological discrimination of GluR5 and GluR6 kainate receptor subtypes by (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole**-5-yl)ethyl]**decahydroisoquinoline-3-carboxylic-acid**  
AUTHOR(S): Bleakman, David; Schoepp, Darryle D.; Ballyk, Barbara; Bufton, Hywel; Sharpe, Erica F.; Thomas, Kathy; Ornstein, Paul L.; Kamboj, Rajender K.  
CORPORATE SOURCE: Eli Lilly and Company, Lilly Research Centre, Windlesham, Surrey, GU20 6PH, UK  
SOURCE: Molecular Pharmacology (1996), 49(4), 581-5  
CODEN: MOPMA3; ISSN: 0026-895X  
PUBLISHER: Williams & Wilkins  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The pharmacol. tools available for the discrimination of kainate receptor subtypes are limited. The authors examd. the effects of (3S,4aR,6R,8aR)-6-[2-(1(2)H-**tetrazole**-5-yl)ethyl]**decahydroisoquinoline-3-carboxylic** acid (LY293558) and 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline (NBQX) on inward currents assocd. with activation of non-N-methyl-D-aspartate (NMDA) receptors in acutely isolated rat cerebellar Purkinje neurons, rat dorsal root ganglion neurons, and human embryonic kidney 293 cells transfected with human glutamate receptors (GluR) 5 and 6. LY293558 and NBQX inhibited kainate-induced currents in cerebellar Purkinje cells, dorsal root ganglion (DRG) neurons, and human GluR5-transfected cells. In contrast, human embryonic kidney 293 cells expressing GluR6 receptors, although blocked by NBQX, were unaffected by LY293558 at concns. of .1 to req. 100 .mu.M. The selective antagonism by LY293558 of GluR5 receptors should allow the detn. of the functional role of GluR5 and GluR6 in more complex systems.

L56 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:10227 HCAPLUS



DOCUMENT NUMBER: 124:106393  
 TITLE: Effects of **decahydroisoquinoline-3-carboxylic acid monohydrate**, a novel AMPA receptor antagonist, on glutamate-induced Ca<sup>2+</sup> responses and neurotoxicity in rat cortical and cerebellar granule neurons

AUTHOR(S): Liljequist, Sture; Cebers, Gvido; Kalda, Anti  
 CORPORATE SOURCE: Department Clinical Neuroscience, Karolinska Institute, Stockholm, S-17176, Swed.

SOURCE: Biochemical Pharmacology (1995), 50(11), 1761-74  
 CODEN: BCPA6; ISSN: 0006-2952

PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB In this study, we examd. the effects of a novel water-sol., putative AMPA receptor antagonist, (-) (3S,4aR,6R,8aR)-6-[2-(1(2H)-**tetrazole-5-yl**)ethyl]-1,2,3,4,4a,5,6,7,8,8a-**decahydroisoquinoline-3-carboxylic acid monohydrate** (LY326325), on glutamate-, N-methyl-D-aspartic acid (NMDA), .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-, and kainic acid (KA)-induced elevations of intracellular Ca<sup>2+</sup> concns. ([Ca<sup>2+</sup>]<sub>i</sub>) and 45Ca<sup>2+</sup> uptake, as well as glutamate agonist-induced neurotoxicity in primary cultures of intact rat cortical and cerebellar granule neurons. In some expts., the actions of LY326325 were tested in the presence of cyclothiazide, a compd. that is known to block glutamate-induced desensitization of AMPA-preferring subtypes of glutamate receptors, thereby largely potentiating the functional effects of AMPA. LY326325 fully blocked the elevations of [Ca<sup>2+</sup>]<sub>i</sub> induced by NMDA and non-NMDA glutamate receptor agonists in both cortical and cerebellar granule neurons. The application of increasing concns. of cyclothiazide was not able to reverse the LY326325-induced blockade of glutamate receptors in cortical neurons. In contrast, the same cyclothiazide treatment fully reversed the blockade produced by the noncompetitive AMPA/KA receptor antagonist 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine HCl (GYKI 52466). In 45Ca<sup>2+</sup> uptake studies. LY325325 inhibited the NMDA-, AMPA-, and KA-induced enhancement of 45Ca<sup>2+</sup> uptake in a concn.-dependent fashion in both cortical and cerebellar granule cells. In analogy to the results obtained with [Ca<sup>2+</sup>]<sub>i</sub> recordings, cyclothiazide failed to counteract the LY326325-induced blockade of KA-stimulated 45Ca<sup>2+</sup> uptake in cerebellar granule neurons, whereas the blockade induced by the noncompetitive AMPA/KA receptor blocking agent GYKI 52466 was fully reversed by cyclothiazide. Because a similar, although no identical pattern of actions was seen following the application of the competitive AMPA/KA receptor antagonist 6-nitro-7-sulphamoyl-benzo(f)quinoxaline-2-3-dione (NBQX), it is suggested that the inhibitory actions of LY326325 are similar to those produced by NBQX but clearly differ from those caused by the noncompetitive AMPA/KA receptor antagonist GYKI 52466. Finally, when the neuroprotective actions of LY326325 on glutamate agonist-induced neurotoxicity were examd. in cerebellar granule neurons, we found that LY326325 almost completely blocked the neurotoxic actions of NMDA, AmPA, and KA, resp., whereas it produced only a partial blockade of glutamate-induced neurotoxicity. Taken together, our current results suggest that although LY326325 blocked both nonNMDA and NMDA-induced Ca<sup>2+</sup> responses, it still displayed a preferential affinity for nonNMDA receptors as compared to NMDA receptors. However, LY326325 appears to be a less selective AMPA/KA receptor antagonist than NBQX and GYKI52466, resp.

L56 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:827899 HCAPLUS  
 DOCUMENT NUMBER: 123:246679  
 TITLE: In vitro and in vivo antagonism of AMPA receptor activation by (3S,4aR,5R,8aR)-6-[2-(1(2H)-**tetrazole-5-yl**)ethyl]

**decahydroisoquinoline-3-carboxylic acid**

AUTHOR(S): Schoepp, D. D.; Lodge, D.; Bleakman, D.; Leander, J. D.; Tizzano, J. P.; Wright, R. A.; Palmer, A. J.; Salhoff, C. R.; Ornstein, P. L.  
 CORPORATE SOURCE: Lilly Res. Lab., Lilly Corporate Center, Indianapolis, IN, 46285, USA  
 SOURCE: Neuropharmacology (1995), 34(9), 1159-68  
 CODEN: NEPHBW; ISSN: 0028-3908  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The in vitro and in vivo pharmacol. of a structurally novel competitive antagonist for the .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subtype of excitatory amino acid receptors is described. LY215490, (.+-.) (6-(2-(1-H-**tetrazol-5-yl**)ethyl) **decahydroisoquinoline-3-carboxylic acid**), was shown to displace selectively 3H-AMPA and 3H-6-cyano-y-nitro-quinoxaline-2,3-dione (3H-CNQX) binding to rat brain membranes. LY215490 potently antagonized quisqualate- and AMPA-induced depolarization of rat cortical slices in a competitive manner, while requiring higher concns. to antagonize the effects of N-methyl-D-aspartate (NMDA) and kainate. In slices of rat hippocampus, LY215490 also selectively antagonized AMPA-evoked release of 3H-norepinephrine. These AMPA receptor activities were due to the (-) isomer of the compd., (3S,4aR,6R,8aR)-6-[2-(1(2-H-**tetrazole-5-yl**)ethyl]**decahydroisoquinoline-3-carboxylic acid** (LY293558). LY215490 was centrally active following parenteral administration in mice as demonstrated by protection vs. maximal electroshock seizures and decreases in spontaneous motor activity. LY215490 (its active isomer being LY293558) represents a novel pharmacol. agent for in vitro and in vivo studies of AMPA receptor function in the CNS.

L56 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:348838 HCAPLUS  
 DOCUMENT NUMBER: 122:151230  
 TITLE: The neuroprotective effects of the **decahydroisoquinoline**, LY 215490; a novel AMPA antagonist in focal ischemia  
 AUTHOR(S): Gill, R.; Lodge, D.  
 CORPORATE SOURCE: R. Vet. Coll., Dep. Vet. Basic Sci., London, NW1 0TU, UK  
 SOURCE: Neuropharmacology (1994), 33(12), 1529-36  
 CODEN: NEPHBW; ISSN: 0028-3908  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB LY 215490 (3RS,4aRS,6RS,8aRS-6-[2-(1(2)H-**tetrazole-5-yl**)ethyl]**decahydroisoquinoline-3-carboxylic acid**), a novel, selective, competitive and systemically active AMPA receptor antagonist was tested as a neuroprotective agent against focal ischemia in a model of permanent MCA occlusion in the rat. LY 215490 was administered at a dose of 10, 30 or 100 mg/kg 30 min prior to and post-MCA occlusion. The animals were allowed to survive for 24 h, following which time the brains were processed for volumetric anal. of the infarct size. The low dose of LY 215490 was not effective against the infarct vol. in the hemisphere, cortex or caudate. The 2 .times. 30 mg/kg dose of LY 215490 resulted in 25 and 31% protection against the vol. of hemispheric and cortical ischemic damage, resp. The highest dose of LY 215490 resulted in a reduced neuroprotective effect with 23 and 27% protection against the vol. of hemispheric and cortical ischemic damage, resp. The slightly reduced neuroprotective effect of the highest dosing regimen may be due to the respiratory problems seen with this dose. Neither of the

two neuroprotective doses of LY 215490 produced any redn. in the vol. of caudate damage which represents the core of the infarct.

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<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

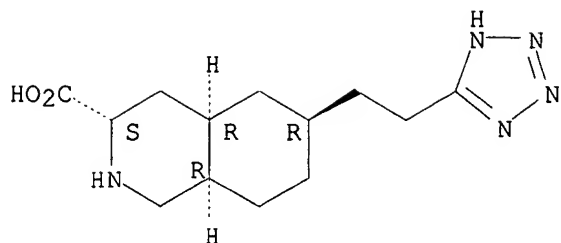
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L57 2 SEA FILE=REGISTRY ABB=ON PLU=ON LY(W) (293558 OR 215490)

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L57 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS  
RN 154652-83-2 REGISTRY  
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-,  
(3S,4aR,6R,8aR)- (9CI) (CA INDEX NAME)  
OTHER CA INDEX NAMES:  
CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-,  
[3S-(3.alpha.,4a.alpha.,6.beta.,8a.alpha.)]-  
OTHER NAMES:  
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FS STEREOSEARCH  
DR 150131-78-5  
MF C13 H21 N5 O2  
CI COM  
SR CA  
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS,  
DRUGNL, DRUGUPDATES, EMBASE, IPA, MEDLINE, PHAR, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (-).



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

58 REFERENCES IN FILE CA (1962 TO DATE)  
58 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:147751  
REFERENCE 2: 138:117562  
REFERENCE 3: 137:273227  
REFERENCE 4: 136:79570  
REFERENCE 5: 136:493  
REFERENCE 6: 135:170886  
REFERENCE 7: 135:137466  
REFERENCE 8: 134:275608  
REFERENCE 9: 134:54906  
REFERENCE 10: 133:305610

L57 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS

RN 150010-68-7 REGISTRY

CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3R,4aS,6S,8aS)-rel- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3.alpha.,4a.alpha.,6.beta.,8a.alpha.)-(.+-.)-

OTHER NAMES:

CN 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1H-tetrazol-5-yl)ethyl]-, (3.alpha.,4a.alpha.,6.beta.,8a.alpha.)-

CN **LY 215490**

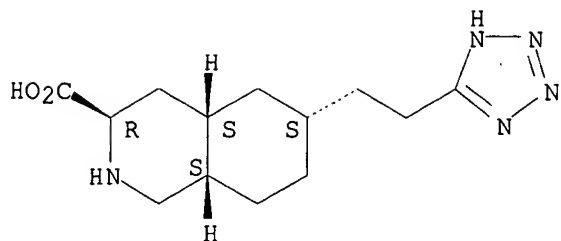
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SR CA

LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, DRUGUPDATES, TOXCENTER, USPATFULL

Relative stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

14 REFERENCES IN FILE CA (1962 TO DATE)  
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 14 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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 REFERENCE 2: 133:247292  
 REFERENCE 3: 132:58931  
 REFERENCE 4: 131:54231  
 REFERENCE 5: 129:23447  
 REFERENCE 6: 128:212404  
 REFERENCE 7: 127:170899  
 REFERENCE 8: 126:1010  
 REFERENCE 9: 123:329860  
 REFERENCE 10: 123:246679

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FILE COVERS 1907 - 7 Mar 2003 VOL 138 ISS 11

FILE LAST UPDATED: 6 Mar 2003 (20030306/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L39 40 SEA FILE=REGISTRY ABB=ON PLU=ON TETRAZOL?(L)ETHYL(L)DECA?(L)CARBOX?

L40 214532 SEA FILE=REGISTRY ABB=ON PLU=ON 3(W)CARBOX?

L41 8 SEA FILE=REGISTRY ABB=ON PLU=ON L39 AND L40

L46 323 SEA FILE=HCAPLUS ABB=ON PLU=ON DECAHYDROISOQUIN?

L49 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L41

L53 66 SEA FILE=HCAPLUS ABB=ON PLU=ON L46 AND 3(W)CARBOX?

L54 40 SEA FILE=HCAPLUS ABB=ON PLU=ON L53 AND TETRA?

L55 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L54 AND TETRAZOLE(W)5

L56 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L55 NOT L49

L57 2 SEA FILE=REGISTRY ABB=ON PLU=ON LY(W)(293558 OR 215490)

L58 64 SEA FILE=HCAPLUS ABB=ON PLU=ON L57

L59 55 SEA FILE=HCAPLUS ABB=ON PLU=ON L58 NOT (L56 OR L49)

L60 18 SEA FILE=HCAPLUS ABB=ON PLU=ON L59 AND (SPIN? OR ANEST? OR PAIN? OR ANALGES?)

=&gt; d ibib abs hitrn 160 1-18

L60 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:570979 HCAPLUS

DOCUMENT NUMBER: 138:117562

TITLE: Effect of intrathecal non-NMDA EAA receptor antagonist LY293558 in rats a new class of drugs for **spinal anesthesia**

AUTHOR(S): Von Bergen, Nicholas H.; Subieta, Alberto; Brennan, Timothy J.

CORPORATE SOURCE: University of Iowa College of Medicine, Iowa City, IA, 52242-1079, USA

SOURCE: Anesthesiology (2002), 97(1), 177-182

CODEN: ANESAV; ISSN: 0003-3022

PUBLISHER: Lippincott Williams &amp; Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Excitatory amino acid receptors are important for both sensory and motor function in the **spinal** cord. We studied the effects of intrathecal LY293558, a competitive non-N-methyl-D-aspartate excitatory amino acid receptor antagonist, on motor and sensory function in rats to det. whether drugs blocking these receptors could potentially be used as alternative agents to local **anesthetics** for **spinal anesthesia**. Rats were tested before and 15-240 min after intrathecal injection of 5 nmol (in 10 .mu.l) LY293558. Sensory function was tested at the hind paw using withdrawal response to pin prick and withdrawal to pinch with sharp forceps. Motor performance (ambulation, placing reflex, and Rotorod time), blood pressure, and heart rate were also evaluated. Some tests were repeated the next day. Responses after LY293558 were compared to injection of 40 .mu.l bupivacaine, 0.75%. Pin-prick responses at the forepaw, chest, abdomen, hind leg, and hind paw were also examd. after intrathecal LY293558. Intrathecal LY293558 blocked both sensory and motor responses through 180 min; complete recovery was present the following day. No change in blood pressure or heart rate occurred. The effects of LY293558 were more pronounced and sustained than those of bupivacaine. Segmental blockade of the response to pin prick was present after LY293558. Drugs like LY293558 that block .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate receptors may be an alternative to local **anesthetics** for **spinal anesthesia** in humans.

IT 154652-83-2, LY293558

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)

(effect of intrathecal non-NMDA EAA receptor antagonist LY293558 in  
rats a new class of drugs for **spinal anesthesia**)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:801702 HCAPLUS

DOCUMENT NUMBER: 136:95462

TITLE: LY-293558 (Eli Lilly & Co)

AUTHOR(S): Gilron, Ian

CORPORATE SOURCE: Departments of Anesthesiology and Pharmacology &  
Toxicology, Kingston General Hospital, Queen's  
University, Kingston, ON, K7L 2V7, Can.

SOURCE: Current Opinion in Investigational Drugs (PharmaPress  
Ltd.) (2001), 2(9), 1273-1278

CODEN: COIDAZ

PUBLISHER: PharmaPress Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Lilly is developing the racemic compd. LY-215490, a selective  
and competitive AMPA antagonist, as a potential treatment for cerebral  
infarction, cerebrovascular ischemia, epilepsy and as an **analgesic**  
[135089], [158980], [254029], [278691]. By Jan. 2000, LY-293558 was  
undergoing phase II trials for **pain** [414000].

IT 150010-68-7, LY-215490

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological  
activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(LY-215490: AMPA antagonist for **analgesia**)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:370555 HCAPLUS

DOCUMENT NUMBER: 136:79570

TITLE: Can novel AMPA and NMDA receptor antagonists induce  
**analgesia**?

AUTHOR(S): Uchikawa, Tomoyoshi; Kiuchi, Yuji; Kindscher, James;  
Oguchi, Katsuji; Goto, Hiroshi

CORPORATE SOURCE: Orthopedic Surgery, Showa University Fujigaoka  
Hospital, Yokohama, 227-8501, Japan

SOURCE: Showa University Journal of Medical Sciences (2000),  
12(3), 235-240

CODEN: SUMSEG; ISSN: 0915-6380

PUBLISHER: Showa Medical Association and Showa University

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The glutamate receptors in the nervous system are related to nociceptive  
response. These receptors include the AMPA (.alpha.-amino-3-hydroxy-5-  
methyl-4-isoxazolepropionate) receptor and the NMDA (N-methyl-D-aspartate)  
receptor. The purpose of this study was to investigate whether novel  
antagonists of these glutamate receptors could inhibit the nociceptive  
response in the **spinal** cord of male Wistar rats. Rats  
intrathecally (i.t.) received 0.1 to 10 pmol of Ly-293558 (a novel AMPA  
antagonist) and 10 to 1000 pmol of Ly-233053 (a novel NMDA antagonist)  
dissolved in 50 .mu.l of physiol. saline. A 50 .mu.l vol. of 2.0%  
formalin soln. was injected as a noxious stimulus into the hindpaw 15 min  
after the i.t. injections. We measured the total time the animal spent  
licking the hindpaw in the first 5 min (early phase) and from 10 to 30 min  
(late phase) after formalin injection. Controlled total licking time was  
103 .+- 13 s (mean .+- SE) (early phase) and 151 .+- 86 s (late phase).  
The licking time during the early phase was significantly and

dose-dependently decreased with intrathecal administrations of both Ly-293558 and Ly-233053 ( $p < 0.05$ ). However, Ly-293558 induced this effect at much lower concns. During the late phase, only the highest dose of each antagonist significantly shortened licking time. Our results indicate that these two novel AMPA and NMDA receptor antagonists when intrathecally administered could induce antinociceptive effects during both the acute phase (peripheral sensitization) and late phase (central sensitization) of formalin-induced nociceptive stimulation without producing motor dysfunction.

IT 154652-83-2, Ly-293558

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(can novel AMPA and NMDA receptor antagonists induce **analgesia**)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:717381 HCAPLUS

DOCUMENT NUMBER: 134:275608

TITLE: Effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative **pain**

AUTHOR(S): Gilron, Ian; Max, Mitchell B.; Lee, Gloria; Booher, Susan L.; Sang, Christine N.; Chappell, Amy S.; Dionne, Raymond A.

CORPORATE SOURCE: Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, the Department of Nursing, NIH Clinical Center, National Institutes of Health, Bethesda, MD, 20892-1258, USA

SOURCE: Clinical Pharmacology & Therapeutics (St. Louis) (2000), 68(3), 320-327  
CODEN: CLPTAT; ISSN: 0009-9236

PUBLISHER: Mosby, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Previous studies suggest that 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate antagonists reduce exptl. induced **pain**. There have been no studies of AMPA/kainate antagonists in clin. **pain**. Methods: **Analgesic** efficacy of i.v. LY293558 (0.4 or 1.2 mg/kg) was compared with that of i.v. ketorolac tromethamine (INN, ketorolac; 30 mg) and placebo in a randomized, double-blind, parallel-group study after oral surgery ( $n = 70$ ). Study drugs were administered at the onset of moderate **pain**; **pain** intensity and relief were measured for 240 min. Results: High-dose LY293558 and ketorolac tromethamine were superior to placebo ( $P < .05$ ) for **pain** evoked by mouth opening and one of several measures of spontaneous **pain**: SPID240  $\pm$  SEM for **pain** evoked by mouth opening was highest for ketorolac tromethamine (151  $\pm$  58), intermediate for high-dose LY293558 (-45  $\pm$  35), and least for low-dose LY293558 (-151  $\pm$  39) and placebo (-162  $\pm$  50). High-dose LY293558 was superior to placebo at individual time points (45 to 240 min) for **pain** evoked by mouth opening but not for spontaneous **pain**. The spontaneous summed **pain** intensity difference over 240 min (SPID240  $\pm$  SEM) was highest for ketorolac tromethamine (303  $\pm$  84), intermediate for high-dose LY293558 (-51  $\pm$  40) and low-dose LY293558 (-96  $\pm$  45), and least for placebo (-180  $\pm$  24). LY293558 was well tolerated, with dose-dependent and reversible side effects including hazy vision in 20% of patients and sedation in 15%. Conclusions: This is the first evidence that an AMPA/kainate antagonist reduces clin. **pain**. Tests of evoked **pain** may be more sensitive to certain **analgesics** than those of spontaneous **pain**. The evaluation of evoked **pain** as an outcome



measure in **analgesic** trials may identify potentially useful compds. otherwise missed if only spontaneous **pain** is evaluated.

IT 154652-83-2, LY293558

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative **pain** in humans)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:263975 HCAPLUS

DOCUMENT NUMBER: 133:38538

TITLE: Effects of glutamate receptor antagonists on lower urinary tract function in conscious unanesthetized rats

AUTHOR(S): Nishizawa, Oamu; Igawa, Yasuhiko; Satoh, Tomoya; Yamashiro, Seiji; Sugaya, Kimio

CORPORATE SOURCE: Department of Urology, Shinshu University School of Medicine, Matsumoto City, 390, Japan

SOURCE: Advances in Experimental Medicine and Biology (1999), 462(Advances in Bladder Research), 275-281  
CODEN: AEMBAP; ISSN: 0065-2598

PUBLISHER: Kluwer Academic/Plenum Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Studies were carried out to study the effects of the intrathecal administered glutamate receptor antagonists on the bladder and urethral activities during isovolumetric bladder contraction in conscious normal and chronic **spinal** rats. Twenty-eight female Wistar rats with and without previous **spinal** cord transection were used. Before and after intrathecal administration of glutamate receptor antagonist, urodynamic parameters under isovolumetric condition of the bladder were analyzed. In normal rats, MK-801 (noncompetitive N-methyl-D-aspartate [NMDA] receptor antagonist) and LY 293558 (competitive AMPA receptor antagonist) produced a decrease in bladder contraction pressure and urethral activity with dose dependent manner. In chronic **spinal** rats, detrusor-sphincter dyssynergia (DSD) was developed before drug administration. MK-801 and LY 293558 partially inhibited bladder contraction pressure, and markedly depressed urethral contraction concomitant with bladder contraction. LY 293558 produced urethral relaxation concomitant with bladder contraction. Thus, in both normal rats and chronic **spinal** rats, two subtypes of glutamate receptors (NMDA and AMPA receptors) in the **spinal** cord were involved in the control of bladder and urethral activities. The AMPA receptor in the **spinal** cord seems to take an important role in the development of DSD.

IT 154652-83-2, LY 293558

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(intrathecal glutamate receptor antagonists effect on bladder and urethral activities during isovolumetric bladder contraction in conscious normal and chronic **spinal** rats)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:34733 HCAPLUS

DOCUMENT NUMBER: 132:88184

TITLE: Inhibitors of the interaction of glutamate with the

AMPA and/or kainate receptor complex for treatment of demyelinating disorders  
 INVENTOR(S): Turski, Lechoslaw; Smith, Terence  
 PATENT ASSIGNEE(S): Eisai Co., Ltd, Japan  
 SOURCE: PCT Int. Appl., 104 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000001376	A2	20000113	WO 1999-GB2112	19990702
WO 2000001376	A3	20010322		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1100504	A2	20010523	EP 1999-929545	19990702
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002519373	T2	20020702	JP 2000-557823	19990702
PRIORITY APPLN. INFO.:				
			GB 1998-14380	A 19980702
			GB 1998-24393	A 19981106
			WO 1999-GB2112	W 19990702

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of demyelinating disorders. Inhibitors of the interaction of glutamate with the AMPA and/or kainate receptor complex are likely to be useful in treating demyelinating disorders and can be formulated as pharmaceutical compns.

IT **154652-83-2**, LY293558  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (inhibitors of interaction of glutamate with AMPA and/or kainate receptor complex for treatment of demyelinating disorders)

L60 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:581904 HCAPLUS  
 DOCUMENT NUMBER: 132:58931  
 TITLE: Influence of Glutamate Receptor Antagonists on Micturition in Rats with **Spinal** Cord Injury  
 AUTHOR(S): Yoshiyama, Mitsuharu; Nezu, Frank M.; Yokoyama, Osamu; Chancellor, Michael B.; de Groat, William C.  
 CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15261, USA  
 SOURCE: Experimental Neurology (1999), 159(1), 250-257  
 CODEN: EXNEAC; ISSN: 0014-4886  
 PUBLISHER: Academic Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB This study was undertaken to det. if an AMPA (LY215490) or an NMDA (MK-801) glutamatergic receptor antagonist can reduce urinary tract dysfunctions related to detrusor hyperreflexia and detrusor-sphincter dyssynergia in awake, **spinal** cord-injured (SCI) rats. Expts. were performed on female Sprague-Dawley rats in which the **spinal** cord was completely transected at T8-10 level, 2-3 wk prior to performing an intravesical continuous infusion cystometrogram (CMG). Bladder vol. threshold (VT) for inducing voiding and voiding efficiency (VE) were detd. by measuring voided vols. and residual vols. (RV). After control CMGs were performed, cumulative i.v. doses of LY215490 (0.1, 1, and 10 mg/kg) or MK-801 (0.03, 0.3, and 3 mg/kg) were administered at 120-min intervals. Small doses of LY215490 (0.1 mg/kg) or MK-801 (0.03 and 0.3 mg/kg) did not

affect any parameters. A large dose (10 mg/kg) of LY215490 decreased maximal voiding pressure (MVP) by 27% and increased RV by 119% and VT by 58% but did not decrease VE. The highest cumulative dose (3 mg/kg) of MK-801 significantly increased RV by 134% and VT by 44% and markedly decreased VE by 60% and MVP by 18%. The effects of LY215490 to reduce MVP and increase VT without changing VE suggest that an AMPA receptor antagonist might be useful in treating detrusor-sphincter dyssynergia and bladder hypertrophy after SCI. The effect of MK-801 to markedly reduce VE indicates that NMDA receptor antagonists may exacerbate neurogenic bladder dysfunction in SCI patients. (c) 1999 Academic Press.

IT 150010-68-7, LY215490

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses).

(influence of glutamate receptor antagonists on micturition in rats with spinal cord injury)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:256179 HCAPLUS

DOCUMENT NUMBER: 131:54231

TITLE: Effects of N-methyl-D-aspartate (dizocilpine) and .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (LY215490) receptor antagonists on the voiding reflex induced by perineal stimulation in the neonatal rat

AUTHOR(S): Yoshiyama, M.; Erickson, K. A.; Erdman, S. L.; De Groat, W. C.

CORPORATE SOURCE: School of Medicine, Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA, 15261, USA

SOURCE: Neuroscience (Oxford) (1999), 90(4), 1415-1420

CODEN: NRSCDN; ISSN: 0306-4522

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The present study was undertaken to examine the role of .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate and N-methyl-D-aspartate glutamate receptors in the regulation of voiding reflexes induced by perineal stimulation in the neonatal rat. Four-, six- and 10-day-old awake rats were used in the expts. and perineal stimulation was applied using the tip of a 1-mL syringe to evoke voiding. Voided vol. and residual vol. were measured. In 10-day-old rats, LY215490 (3-10 mg/kg, i.p.), a competitive .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor antagonist, significantly inhibited reflex voiding, increasing the residual vol. 34-53-fold. A 3 mg/kg dose decreased the urine release by 55%, whereas 10 mg/kg totally suppressed the voiding reflex induced by the perineal stimulation. LY215490 (10 mg/kg, i.p.) produced similar effects in four- and six-day-old rats. Dizocilpine (1-3 mg/kg, i.p.), a non-competitive N-methyl-D-aspartate receptor antagonist, also significantly decreased the urine release (62-82%) and increased residual vol. (180-230-fold). Combined administration of LY215490 (1 mg/kg, i.p.) and dizocilpine (0.3 mg/kg, i.p.) to 10-day-old rats, in doses that individually had no effect on perineal stimulation-evoked voiding, depressed voided vol. by 65%. These results indicate that, in neonatal rats, glutamatergic transmission in the spinal cord has an essential role in reflex micturition induced by perineal stimulation, and that facilitatory interactions between .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate and N-methyl-D-aspartate glutamatergic mechanisms are important for voiding, as noted previously in adult rats.

IT 150010-68-7, LY215490

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(glutamatergic receptor in regulation of micturition induced by  
perineal stimulation in development response to)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:779038 HCAPLUS  
DOCUMENT NUMBER: 130:134099  
TITLE: Decahydroisoquinolines: novel competitive AMPA/kainate  
antagonists with neuroprotective effects in global  
cerebral ischemia  
AUTHOR(S): O'Neill, Michael J.; Bond, Ann; Ornstein, Paul L.;  
Ward, Mark A.; Hicks, Caroline A.; Hoo, Ken; Bleakman,  
David; Lodge, David  
CORPORATE SOURCE: Lilly Research Centre, Eli Lilly and Co. Ltd.,  
Windlesham, GU20 6PH, UK  
SOURCE: Neuropharmacology (1998), 37(10-11), 1211-1222  
CODEN: NEPHBW; ISSN: 0028-3908  
PUBLISHER: Elsevier Science Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB In the present study, the activity of a series of glutamate receptor  
antagonists from the decahydroisoquinoline group of compds. both in vitro  
and in vivo, are evaluated. Compd. activity at .alpha.-amino-3-hydroxy-5-  
methylisoxazole-4-propionic acid (AMPA) and kainate receptors was assessed  
using ligand binding to cloned iGluR2 and iGluR5 receptors and on  
responses evoked by AMPA and N-methyl-D-aspartate (NMDA) in the cortical  
wedge prepn. In vivo, compds. were examd. for antagonist activity  
electrophysiol. in the rat **spinal** cord prepn. and in the gerbil  
model of global cerebral ischemia. Compds. tested were LY293558, which  
has been shown to protect in models of focal cerebral ischemia, LY202157  
(an NMDA antagonist), LY246492 (an NMDA and AMPA receptor antagonist),  
LY302679, LY292025, LY307190, LY280263, LY289178, LY289525, LY294486  
(AMPA/kainate antagonists) and LY382884 (an iGluR5 selective antagonist).  
Results obtained support a role for AMPA receptors in cerebral ischemia.  
LY377770 (a mixed AMPA/iGluR5 antagonist and active isomer of LY294486)  
demonstrated good neuroprotection with a 2-h time window and may therefore  
be useful in the treatment of ischemic conditions.

IT 154652-83-2, LY 293558  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); BIOL (Biological study)  
(decahydroisoquinoline competitive AMPA/kainate antagonists with  
neuroprotective effects in global cerebral ischemia)

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:763613 HCAPLUS  
DOCUMENT NUMBER: 130:163073  
TITLE: AMPA/kainate antagonist LY293558 reduces  
capsaicin-evoked hyperalgesia but not **pain**  
in normal skin in humans  
AUTHOR(S): Sang, Christine N.; Hostetter, Meredith P.; Gracely,  
Richard H.; Chappell, Amy S.; Schoepp, Darryle D.;  
Lee, Gloria; Whitcup, Scott; Caruso, Rafael; Max,  
Mitchell B.  
CORPORATE SOURCE: NIDR/NIH Pain Research Clinic, Pain and Neurosensory  
Mechanisms Branch, National Institute of Dental  
Research, National Institutes of Health, Bethesda, MD,  
USA  
SOURCE: Anesthesiology (1998), 89(5), 1060-1067  
CODEN: ANESAV; ISSN: 0003-3022  
PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Animal studies suggest that .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-kainate (AMPA-KA) receptors are involved in **pain** processing. The effects of the competitive AMPA-KA antagonist LY293558 in two types of exptl. **pain** in human volunteers, brief **pain** sensations in normal skin, and mech. allodynia-pinprick hyperalgesia were studied after the injection of intradermal capsaicin. Brief i.v. infusions of the competitive AMPA-KA antagonist LY293558 were given to 25 healthy volunteers to examine acute toxicity and **analgesic** effects. Fifteen volunteers then entered a double-blinded, three-period crossover study. In a Phase II study, LY293558 infusions (100% maximally tolerated dose vs. 33% maximally tolerated dose vs. placebo) began 10 min after intradermal injection of 250 .mu.g capsaicin in volar forearm. Spontaneous **pain**, areas of mech. allodynia and pinprick hyperalgesia, and side effects were detd. every 5 min for 60 min. The median maximally tolerated dose was 1.3+-.0.4 (range, 0.9-2.0) mg/kg. Tests of cognitive and neurol. function were unchanged. Dose-limiting side effects were hazy vision in 95% of volunteers and sedation in 40%. There were no significant changes in elec. or warm-cool detection and **pain** thresholds or heat **pain** thresholds. LY293558 had little effect on brief **pain** sensations in normal skin. Both high and low doses of LY293558 significantly reduced **pain** intensity, **pain** unpleasantness, and the area in which light brush evoked **pain** after intradermal capsaicin. There was a trend toward a dose-response effect of LY293558 on the area in which pinprick evoked **pain** after intradermal capsaicin, which did not reach statistical significance. The authors infer that AMPA-KA receptor blockade reduces the **spinal** neuron sensitization that mediates capsaicin-evoked **pain** and allodynia. The low incidence of side effects at EDs of LY293558 suggests that this class of drugs may prove to be useful in clin. **pain** states.

IT 154652-83-2, LY293558

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(AMPA/kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not **pain** in normal skin in humans)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:441022 HCAPLUS

DOCUMENT NUMBER: 129:170935

TITLE: Kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat

AUTHOR(S): Simmons, Rosa Maria A.; Li, Dominic L.; Hoo, Ken H.; Deverill, Michelle; Ornstein, Paul L.; Iyengar, Smriti

CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly, Lilly Corporate Center, Indianapolis, IN, 46285, USA

SOURCE: Neuropharmacology (1998), 37(1), 25-36

CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To study the roles of the AMPA and kainate subtypes of non-NMDA glutamate receptors in the processing of persistent nociceptive information, compds. with varying activities at these receptors were examd. for effects on the formalin-induced paw-licking behavior in rats. The selective AMPA antagonist, LY300164 and the mixed AMPA/kainate antagonist, NBQX, were compared for their effects on formalin-induced **pain** behavior. NBQX (3, 10, 20 mg/kg, i.p.), caused antinociception as well as ataxia,

whereas the selective AMPA antagonist, LY300164 (3,5,10 mg/kg, i.p.), did not cause antinociception at doses that did not produce ataxia. In view of the well documented distribution of kainate receptors on C fibers and of the kainate-preferring iGluR5 subtype on dorsal root ganglia (DRG), the authors tested a series of three decahydroisoquinolines with different profiles of activity between iGluR5 and AMPA receptors and all without activity on iGluR6, iGluR7 or KA2 subtypes. LY293558 (0.1, 1, 3, 5 mg/kg, i.p.), which had low micromolar affinity for both iGluR5 and 2 caused, like NBQX, both antinociceptive and ataxic effects. However, the selective iGluR5 antagonist LY382884 (5, 10, 30, 100 mg/kg, i.p.), exhibited antinociceptive actions without ataxia while the iGluR2 preferring antagonist LY302679 (5 mg/kg, i.p.), caused ataxia but did not produce antinociceptive effects at that dose. These actions were stereoselective since the enantiomeric compds., LY293559 and LY302680, were ineffective in these tests. The data strongly suggest an involvement of iGluR5 in the processing of nociceptive information.

IT 154652-83-2, LY 293558

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:323132 HCAPLUS

DOCUMENT NUMBER: 129:23447

TITLE: A method for treating tension-type headache

INVENTOR(S): Olesen, Jes; Bendtsen, Lars; Jensen, Rigmor; Madsen, Ulf

PATENT ASSIGNEE(S): Olesen, Jes, Den.; Bendtsen, Lars; Jensen, Rigmor; Madsen, Ulf

SOURCE: PCT Int. Appl., 142 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9819674	A2	19980514	WO 1997-DK502	19971104
WO 9819674	A3	19980716		
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
AU 9748632	A1	19980529	AU 1997-48632	19971104
AU 734490	B2	20010614		
EP 1011656	A2	20000628	EP 1997-911150	19971104
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
EP 1132082	A1	20010912	EP 2000-204625	19971104
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
US 6284794	B1	20010904	US 1999-304115	19990504
US 2002072543	A1	20020613	US 2001-941855	20010830
PRIORITY APPLN. INFO.:			DK 1996-1243	A 19961105

US 1996-30294P P 19961105  
 EP 1997-911150 A3 19971104  
 WO 1997-DK502 W 19971104  
 US 1998-85413P P 19980514  
 US 1999-304115 A3 19990504

AB Tension-type headache is treated by interacting with neuronal transmission in relation to **pain** in connection with headache in a way which prevents or decreases sensitization of second order nociceptive neurons. In particular, treatment is performed by administration of an effective amt. of a substance which prevents or decreases central sensitization. Important examples of such substances are substances which interact with glutamate neurotransmission, such as glutamate receptor antagonists. Other examples are e.g. substances which interact with nitric oxide, such as nitric oxide synthase (NOS) inhibitors. According to a broader aspect of the invention, tension-type headache is treated by administration of substances which are effective in preventing or decreasing **pain** in connection with tension-type headache. An addnl. aspect of the invention relates to treatment of tension-type headache by administration of substances which substantially inhibit the activity of NOS. Evidence for central sensitization in chronic myofascial **pain**, as well as mechanisms of spontaneous tension-type headaches, are also described. Gabapentin and dextromethorphen had a prophylactic effect on chronic tension-type headaches.

IT 150010-68-7, LY 215490 150010-68-7D, LY 215490, derivs.  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (tension-type headache treatment)

L60 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:26492 HCAPLUS

DOCUMENT NUMBER: 128:149482

TITLE: The competitive .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor antagonist LY293558 attenuates and reverses **analgesic** tolerance to morphine but not to delta or kappa opioids

AUTHOR(S): Kest, Benjamin; McLemore, Gabrielle; Kao, Bernard; Inturrisi, Charles E.

CORPORATE SOURCE: Department of Pharmacology, Cornell University Medical College, New York, NY, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 283(3), 1249-1255  
 CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Antagonists of the NMDA type of excitatory amino acid (EAA) receptor attenuate or reverse the development of tolerance to the **analgesic** effects of the .mu. opioid agonist morphine, the .delta.-1 opioid agonist DPDPE but not the .kappa.-1 agonist U50488H or the .kappa.-3 agonist naloxone benzoylhydrazone. The role of the AMPA subtype of EAA receptor in **analgesic** tolerance was examd. using LY293558, a selective competitive antagonist that is active after systemic administration. Administration of morphine, DPDPE, or U50488H three times daily for 3 days according to an escalating dosing schedule resulted in **analgesic** tolerance as indicated by an increase in **analgesic** ED50 values using the tail-flick test in mice. **Analgesic** tolerance was attenuated when mice received a continuous s.c. infusion of LY293558 at doses of 30, 45 or 60 mg/kg/24 h via an osmotic pump concurrent with the morphine treatment. Continuous s.c. infusion of LY293558 (45 mg/kg/24 h) also reversed established morphine tolerance. In contrast, continuous s.c. infusion of the highest dose of LY293558 (60 mg/kg/24 h) was

ineffective in preventing the development of **analgesic** tolerance to DPDPE or U50488H. Continuous s.c. infusion of LY293558 (60 mg/kg/24 h) for 3 days protected mice from generalized convulsions produced by the selective AMPA agonist ATPA, indicating that the dosage of LY293558 that attenuated morphine tolerance was effective as an antagonist at AMPA receptors. These results demonstrate that AMPA receptors may play a role in the development and maintenance of morphine, but not DPDPE or U50488H, **analgesic** tolerance.

IT 154652-83-2, LY293558

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(competitive AMPA receptor antagonist LY293558 attenuation and reversal of **analgesic** tolerance to .mu. opioid but not to .delta. or .kappa. opioids)

L60 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:795591 HCAPLUS

DOCUMENT NUMBER: 128:123724

TITLE: The effects of LY293558, an AMPA receptor antagonist, on acute and chronic morphine dependence

AUTHOR(S): McLemore, Gabrielle L.; Kest, Benjamin; Inturrisi, Charles E.

CORPORATE SOURCE: York Avenue, LC-524, Department of Pharmacology, Cornell University Medical College, New York, NY 10021, 1300, USA

SOURCE: Brain Research (1997), 778(1), 120-126

CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In rodents, noncompetitive and competitive NMDA receptor antagonists have been shown to attenuate and, in some cases, reverse tolerance to the **analgesic** effects of morphine. However, the ability of these same excitatory amino acid (EAA) receptor antagonists to modulate morphine dependence is controversial, and very little is known about the role of AMPA receptors in morphine dependence. LY293558, a novel, systemically active, competitive AMPA receptor antagonist and the NMDA receptor antagonists, MK-801 and/or LY235959, were evaluated in tolerant or dependent CD-1 mice. In mice rendered tolerant by morphine injection or pellet implantation, continuous s.c. infusion of LY293558 (60 mg/kg per 24 h) or MK-801 (1 mg/kg per 24 h) attenuated the development of tolerance. Neither LY293558 nor MK-801 produced **analgesia** or altered the ED50 value of morphine. Continuous s.c. infusion of LY293558 (60 mg/kg per 24 h), MK-801 (1 mg/kg per 24 h) or LY235959 (12 mg/kg per 24 h) attenuated the development of acute (3 h) morphine dependence (i.e., decreased naloxone-pptd. withdrawal jumping). In contrast, continuous s.c. infusion of LY293558 (60 mg/kg per 24 h) or LY235959 (12 mg/kg per 24 h) did not significantly attenuate the development of chronic dependence produced by morphine pellet implantation. These data indicate that the development of morphine tolerance is more sensitive to modulation by EAA receptor antagonists than is the development of morphine dependence as assessed by naloxone-pptd. withdrawal jumping.

IT 154652-83-2, LY293558

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of AMPA and NMDA receptor antagonists on acute and chronic morphine dependence)

L60 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:213193 HCAPLUS

DOCUMENT NUMBER: 126:288414

TITLE: L-trans-Pyrrolidine-2,4-dicarboxylic acid-evoked striatal glutamate levels are attenuated by calcium



reduction, tetrodotoxin, and glutamate receptor blockade

AUTHOR(S): Rawls, Scott M.; McGinty, Jacqueline F.

CORPORATE SOURCE: Department of Anatomy and Cell Biology, East Carolina University School of Medicine, Greenville, NC, 27858-4354, USA

SOURCE: Journal of Neurochemistry (1997), 68(4), 1553-1563  
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Lippincott-Raven

DOCUMENT TYPE: Journal

LANGUAGE: English

AB L-trans-Pyrrolidine-2,4-dicarboxylic acid (L-trans-PDC) reverses plasma membrane glutamate transporters and elevates extracellular glutamate levels in vivo. We investigated the possibility that L-trans-PDC-stimulated glutamate levels are mediated partially by increases in transsynaptic activity. Therefore, the degree to which L-trans-PDC-evoked glutamate levels depend on calcium, sodium-channel activation, and glutamate-receptor activation was investigated by infusing via reverse microdialysis (a) 0.1 mM calcium, (b) 1  $\mu$ M tetrodotoxin, a selective blocker of voltage-dependent sodium channels, (c) R(-)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), a selective NMDA-receptor antagonist, or (d) LY293558, a selective  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate antagonist. In sep. exptl. groups, L-trans-PDC-evoked glutamate levels were reduced significantly by 55% in the presence of 0.1 mM calcium and by 46% in the presence of tetrodotoxin. Addnl., CPP and LY293558 significantly attenuated L-trans-PDC-evoked glutamate levels without altering basal glutamate levels. These data suggest that glutamate transporter reversal by L-trans-PDC initially elevates extracellular glutamate levels enough to stimulate postsynaptic glutamate receptors within the striatum. It is proposed that glutamate-receptor stimulation activates a pos. feedback loop within the basal ganglia, leading to further glutamate release from corticostriatal and thalamostriatal afferents. Therefore, either extracellular striatal calcium redn. or tetrodotoxin perfusion leads to decreased action potential-dependent glutamate release from these terminals. In addn., blocking glutamate receptors directly reduces medium **spiny** neuronal firing and indirectly attenuates corticostriatal and thalamostriatal activity, resulting in an overall depression of L-trans-PDC-stimulated glutamate levels.

IT 154652-83-2, LY293558  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(pyrrolidinedicarboxylate-evoked striatal glutamate levels are attenuated by calcium redn., tetrodotoxin, and glutamate receptor blockade)

L60 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:691762 HCAPLUS

DOCUMENT NUMBER: 126:181183

TITLE: A selective AMPA antagonist, LY293558, suppresses morphine withdrawal-induced activation of locus coeruleus neurons and behavioral signs of morphine withdrawal

AUTHOR(S): Rasmussen, Kurt; Kendrick, William T.; Kogan, Jeffrey H.; Aghajanian, George K.

CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN, 46285, USA

SOURCE: Neuropsychopharmacology (1996), 15(5), 497-505  
CODEN: NEROEW; ISSN: 0893-133X

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The glutamate receptor subtype that mediates the morphine

withdrawal-induced activation of locus coeruleus (LC) neurons was examd. in this study using in vitro and in vivo single-unit electrophysiol. recordings. For LC neurons recorded in vitro in rat brain slices, the selective .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonist, LY293558, showed a greater than 10-fold selectivity for inhibiting the excitatory effects of AMPA vs. kainate, and a greater than 30-fold selectivity for inhibiting the excitatory effects of AMPA vs. NMDA. LY293558 also greatly reduced the response of LC neurons to glutamate in a concn.-dependent manner. In in vivo recordings in **anesthetized** rats, pretreatment with LY293558 (0.1 to 10 mg/kg, IP) dose dependently suppressed the morphine withdrawal-induced activation of LC neurons. In unanesthetized, morphine-dependent animals, pretreatment with LY293558 (1 to 30 mg/kg, IP) dose dependently suppressed naltrexone-pptd. morphine withdrawal signs. These results indicate: (1) AMPA receptors mediate a large component of the excitatory effects of glutamate on LC neurons; (2) activation of AMPA receptors plays an important role in the morphine withdrawal-induced activation of LC neurons; (3) AMPA antagonists can suppress many signs of morphine withdrawal in awake animals; and (4) AMPA antagonists may have therapeutic effects in humans for the treatment of opiate withdrawal.

IT 154652-83-2, LY293558

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(AMPA antagonist LY293558 suppresses morphine withdrawal-induced activation of locus coeruleus neurons and behavioral signs of morphine withdrawal)

L60 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:586657 HCAPLUS

DOCUMENT NUMBER: 125:238444

TITLE: The AMPA antagonist LY293558 improves functional neurological outcome following reversible **spinal** cord ischemia in rabbits

AUTHOR(S): Bowes, Mark P.; Swanson, Steven; Zivin, Justin A.

CORPORATE SOURCE: School Medicine, University California, La Jolla, CA, 92093-0624, USA

SOURCE: Journal of Cerebral Blood Flow and Metabolism (1996), 16(5), 967-972

CODEN: JCBMDN; ISSN: 0271-678X

PUBLISHER: Lippincott-Raven

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Glutamate (Glu) neurotoxicity is an important element of a no. of neurol. disorders including central nervous system (CNS) ischemia. We evaluated the effects of the novel AMPA Glu antagonist LY293558 on functional neurol. outcome in two rabbit stroke models. In the reversible **spinal** cord ischemia model, ischemia of the caudal lumbar **spinal** cord was produced by temporary occlusion of the abdominal aorta. LY293558 was administered 5 min after recirculation as a 16 mg/kg i.v. bolus followed by 2.2 mg/kg infused over 1 h. Control animals received saline. LY293558 significantly increased the duration of ischemia required to produce paraplegia, from 30.5 +/- 15.8 min (mean +/- SD) controls to 50.1 +/- 11.5 in treated animals (p < 0.01). In an irreversible model of cerebral ischemia, 50 .mu.m plastic microspheres were injected into the carotid artery and lodged in the cerebral microvasculature. LY293558 did not significantly reduce neurol. damage in this model. These data suggest that LY293558 may have therapeutic benefit following some types of ischemic injury.

IT 154652-83-2, LY293558

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(AMPA antagonist LY293558 improves functional neurol. outcome following reversible **spinal** cord ischemia)

L60 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:525011 HCAPLUS

DOCUMENT NUMBER: 121:125011

TITLE: Neuroprotective effect of the AMPA receptor antagonist LY-293558 in focal cerebral ischemia in the cat

AUTHOR(S): Bullock, R.; Graham, D. I.; Swanson, S.; McCulloch, J.

CORPORATE SOURCE: Wellcome Surg. Inst. and Hugh Fraser Neurosci. Lab., Univ. Glasgow, Glasgow/Scotland, G61 1QH, UK

SOURCE: Journal of Cerebral Blood Flow and Metabolism (1994), 14(3), 466-71

CODEN: JCBMDN; ISSN: 0271-678X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of the glutamate .alpha.-amino-3-hydroxy 5-methyl-4-isoxazole propionate (AMPA) receptor antagonist LY-293558 in reducing ischemic brain damage have been assessed in halothane-**anesthetized** cats. Focal cerebral ischemia was produced by permanent occlusion of one middle cerebral artery, and the animals were killed 6 h later. The amt. of early irreversible ischemic damage was assessed at 16 predetd. stereotactic planes by an observer blinded to treatment paradigm employed. Treatment with LY-293558 (15 mg/kg i.v., plus infusion of 7 mg/kg/h) initiated 30 min prior to middle cerebral artery occlusion reduced significantly ( $p < 0.02$ ) the vol. of ischemic damage (from 3,423  $\pm$  212 mm<sup>3</sup> of the cerebral hemisphere in vehicle-treated cats to 2,822  $\pm$  569 mm<sup>3</sup> in LY-293558-treated cats). The present data demonstrate that an AMPA receptor antagonist can reduce focal ischemic damage in a gyrencephalic species in which key physiol. variables have been controlled and monitored throughout the postischemic period. These data provide addnl. support for the clin. evaluation of AMPA receptor antagonists in focal cerebral ischemia in humans.

IT **154652-83-2**, LY-293558

RL: PRP (Properties)

(neuroprotective effect of, in focal cerebral ischemia)